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| 10/585,504 | 02/14/2008 | Haofun Jin | 587.PFUS | 7676 |
| 25000 7590 09/26/2008 GILEAD SCIENCES INC 333 LAKESIDE DR FOSTER CITY, CA 94404 | | | | |
| EXAMINER MCDOWELL, BRIANE | | | | |
| ART UNIT | | PAPER NUMBER | | |
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| MAIL DATE | | DELIVERY MODE | | |
| 09/26/2008 | | PAPER | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/585,504

Applicant(s)

JIN ET AL.

Examiner

BRIAN MCDOWELL

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/1/2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-46 is/are pending in the application.
- 4a) Of the above claim(s) 2-7, 9, 11, 12, 15, 19, 20, 22-36, 38-40, and 42-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 8, 10, 13, 14, 16-18, 21, 37 and 41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

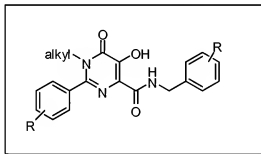
Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 8/1/2008.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

BEM

DETAILED ACTION**RESPONSE TO ELECTION/RESTRICTION**

Applicant's election without traverse of group I (see below, wherein R^1 = substituted aryl group, $R^3 = R^5 = H$, and $R^{2b} = C_1 - C_{18}$ alkyl) and election of specie (specie set forth in claim 37) in the reply filed on 8/1/2008 is acknowledged. Claims 1,8,10,13,14,16-18,21,37, and 41 read on the elected specie.



Claims 2-7,9,11,12,15,19,20,22-36,38-40, and 42-46 (claims 44-46 are not drawn to compound claims) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

This application contains claims drawn to an invention nonelected without traverse in the reply filed on 8/1/2008. A complete reply to this action must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

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An action on the merits of claims 1,8,10,13,14,16-18,21,37, and 41 is contained herein.

Priority

This application is a national stage entry of PCT/US2005/000815, which claims priority to provisional application 60/536010, filed on 1/12/2004. However, a claim to domestic priority was not cited in the specification or ADS, hence the effective filing date of this application is 11/01/2005.

Applicant is reminded of the following requirement:

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application

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which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a)

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(e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1,8,10,13,14,16-18,21,37, and 41 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1,8,10,13,14,16-18,21,37, and 41 of copending Application No. 11/033422. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

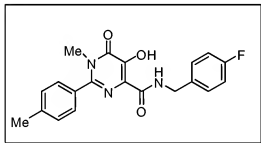
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,10,14,16-18,21, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated over Crescenzi *et al.* (WO 03/035077-mentioned in IDS).

The aforementioned claims refer to compounds of the formula II.

Crescenzi *et al.* teach the following compound (see page 146, example 18):



Wherein R^{2b} = methyl, R^1 = substituted aryl, $R^3 = R^5 = H$, and R^4 = substituted alkyl (via substituted aryl ring) that read on the aforementioned claims and are therefore anticipated.

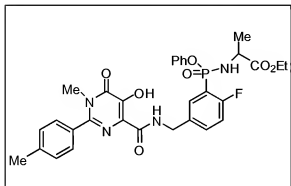
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1,8,10,13,14,16-18,21,37, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crescenzi *et al.* (WO 03/035077-mentioned in IDS) in view of Banker *et al.* (Modern Pharmaceuticals) and McGuigan *et al.* (WO 00/18775).

The above claims are drawn to applicant's elected compound below:



Crescenzi *et al.* taught what was stated previously.

However, this document does not teach this compound possessing the phosphoramidate moiety (prodrug substituent).

McGuigan *et al.* teach prodrugs that possess phosphoramidate moieties (particularly the phenyl(methoxy-L-valinyl phosphate) that act as effective agents against DNA viruses such as HIV (see abstract and page 77, compound Cf1686).

Lastly, Banker *et al.* teach that prodrugs may modify the physiochemical properties of the drug, usually resulting in a change of permeability and localization of the drug (see page 596, second sentence).

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The only difference between applicant's compound and the compound described by Crescenzi *et al.* is the lack or presence of the phosphoramidate moiety (prodrug substituent). In summary, applicant is simply modifying a known compound and placing a well-known phosphoramidate moiety on the molecule (i.e., making a prodrug). Additionally, both compounds have the same utility (HIV agents) and it would have been *prima facie* obvious for one of ordinary skill in the art based on the teachings of Banker and McGuigan to introduce this particular hydrolyzable phosphoramidate moiety and expect a compound with similar biological activity.

Therefore, applicant's compounds are obvious over the prior art and are rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,8,10,13,14,16-18,21,37, and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making compounds with prodrug moieties bearing phosphonates and phosphoramidates, it does not reasonably provide enablement for making every prodrug moiety of the claimed compounds.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Pursuant to *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444. Analysis is described below:

(A) Breadth of claims: The breadth of the claims encompass any of the tens of thousands of compounds possessing prodrug moieties represented by applicant's elected invention, thus the claims are very broad.

(B) The nature of the invention: Pyrimidyl phosphonate compounds.

(C) State of the Prior Art: Chemistry is unpredictable. See *In Re Marzocchi* and *Horton* 169 USPQ at 367 paragraph 3:

"Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of

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successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.

Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such workChemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)" Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

(D) Skill of those in the art: The level of skill in the art is high.

(E) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an

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unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(F) Direction or Guidance: Little guidance or direction is provided by applicant in reference to making compounds with prodrug moieties other than those containing phosphonates and phosphonamides.

(G) Working Examples: The compound core depicted with specific substituents represent a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed. Applicant has provided no working examples of any compounds where the compound of formula (II) did not contain the prodrug moieties previously mentioned above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

(H) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome. Applicant fails to provide guidance and supporting

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information for making the thousands of other compounds which are encompassed by the claims, therefore undue experimentation would be expected.

Due to the level of unpredictability in the art, the very limited guidance provided, and the lack of working examples, the applicant has shown lack of enablement. MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN MCDOWELL whose telephone

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number is (571)270-5755. The examiner can normally be reached on Monday-Thursday 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BM

/Patrick J. Nolan/

Supervisory Patent Examiner, Art Unit 4161